REMARKS

A check in the amount of $530.00 for a third month's extension of time ($950.00 minus $420.00 previously paid on October 14, 2003) is enclosed. Any fee that may be due in connection with the filing of this paper may be charged to Deposit Account No. 50-1213. If a Petition for Extension of Time is needed, this paper is to be considered such Petition.

Applicant filed a Notice of Appeal on October 14, 2003. An Appeal Brief will be submitted in due course.

Claims 1-64, 69-83, 87-89, 93 and 99-121 are pending herein. No amendments to the claims are made herein.

REJECTION OF CLAIMS 1-64, 69-83, 87-89, 99-112 AND 117-119 UNDER 35 U.S.C. §103(a)

Claims 1-64, 69-83, 87-89, 99-112 and 117-119 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.* (U.S. Patent No. 6,150,418) in view of Bartow *et al.* ((1998) *Drugs 55(2)*:303-322) and the Physician's Desk Reference (PDR) entry for fluticasone propionate. Applicant respsectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

[I]n order to establish a prima facie case of obviousness, there must be evidence, preferably a teaching, suggestion, incentive or inference from the cited art or in the form of generally available knowledge that one of ordinary skill would have been led to modify the relevant teaching to arrive at what is claimed. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

In addition, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed subject matter. See, *e.g., W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). A *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. See, *e.g., In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

The instant claims

Instant claim 1 is directed to a pharmaceutical composition, containing (i) formoterol, or a derivative thereof; and (ii) a steroidal anti-inflammatory agent, or a derivative thereof; in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Claims 2-64, 69-76, 81-83, 87-89, 99-108, 111 and 112 are all dependent on claim 1 and therefore incorporate all of the limitations of claim 1.

Claim 77 is directed to a nebulized suspension or solution, containing (i) formoterol or a derivative thereof; and (ii) a steroidal anti-inflammatory agent, or a derivative thereof; in a pharmacologically suitable fluid.

Claim 78 is directed to a kit, containing (a) an aqueous composition containing (i) formoterol or a derivative thereof, and (ii) a steroidal anti-inflammatory agent or a derivative thereof, formulated for single dosage administration; and (b) a nebulizer. Claims 79-80, 109 and 110 are dependent on claim 78 and therefore incorporate all of the limitations of claim 78.

Claim 117 is directed to a combination, containing a composition containing formoterol, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the

composition is formulated at a concentration for direct administration to a subject in need thereof; and a composition containing a bronchodilating steroid, or a derivative thereof.

Differences between the cited references and the instant claims

Hochrainer *et al.*

Applicant has previously argued, *inter alia*, that Hochrainer *et al.* teaches two compositions: 1) an "active substance concentrate;" and 2) a "pharmaceutical preparation." The cited reference teaches that the "active substance concentrate" is not formulated at a concentration for direct administration, but must be diluted prior to administration to form the "pharmaceutical preparation" (see, *e.g.*, column 4, lines 9-13). Applicant has further argued, *inter alia*, that Example 3 of Hochrainer *et al.* teaches that the "pharmaceutical preparation," which is formulated at a concentration for direct administration to a subject in need thereof, is not stable during long term storage. Therefore, the cited reference, in combination with the other cited references, does not teach or suggest the instantly claimed stable aqueous formoterol/steroid compositions, which are formulated at a concentration for direct administration to a subject in need thereof.

The Advisory Action alleges that Example 3 of Hochrainer *et al.* merely teaches that formoterol aqueous solutions are not stable during long term storage, while formoterol aqueous suspensions are stable during long term storage. It is further alleged that the instant claims read on both suspensions and solutions, and therefore are allegedly obvious in view of the cited references. While Applicant recognizes that the Office admits the patentability of the instant claims if restricted to solutions, Applicant strongly believes that suspensions within the scope of the instant claims are also patentable over the teachings of the cited references. Applicant respectfully disagrees with the Office's interpretation of Example 3 of Hochrainer *et al.* and requests reconsideration in view of the following remarks.

Example 3 of Hochrainer *et al.*

Example 3 of Hochrainer *et al.* recites as follows:

> In an aqueous solution with a pH of 5.0, formoterol breaks down to 10% at 40° C. within only 3 months. In a comparable suspension,

> no breakdown of any kind can be observed even after 6 months' storage at 40° C.

When read in the context of the Hochrainer *et al.* reference, *i.e.*, when the reference is read as a whole, this Example teaches more than a mere difference in stability between formoterol solutions and suspensions. The cited reference teaches that the "active substance concentrate" provided therein is stable during long term storage. See, *e.g.*, column 1, lines 55-61:

> The active substance concentrate according to the invention refers to...suspensions...which are characterized in that the active substance, formoterol, can be stored therein for a period from several months possibly up to several years without any deterioration in the pharmaceutical quality.

Therefore, the suspension of Example 3, which is stable for at least 6 months, must be an example of the "active substance concentrate" of Hochrainer *et al.*

The reference also teaches that the "active substance concentrate" is not formulated at a concentration for direct administration to a subject in need thereof, but must be diluted prior to administration. See, *e.g.*, column 4, lines 9-13:

> The active substance concentrate according to the invention is not usually suitable as such for direct medicinal use, particularly for inhalation. As already explained, use of the active substance concentrate comprises converting it into a pharmaceutical preparation (aerosol formulation).

See also, *e.g.*, column 1, lines 55-57:

> The active substance concentrate according to the invention refers to...suspensions in which formoterol is...suspended in highly concentrated form...

See also, *e.g.*, column 2, lines 2-7:

> The term "highly concentrated" means a concentration of the active substance which is usually too high to enable the corresponding...suspension to be used therapeutically for inhalation without being diluted. According to the invention the formoterol concentration in the active substance concentrate is between 10 mg/ml and 500 mg/ml. Preferably, the minimum concentration is at least 75 mg/ml.

The instantly-claimed compositions are formulated at a lower formoterol concentration (*e.g.*, a concentration for direct administration to a subject in need thereof), and do not require dilution prior to administration. The reference does not teach or suggest formoterol formulations, including formoterol suspension formulations, at this lower concentration that are stable during long term storage.

Therefore, Hochrainer *et al.* does not teach or suggest stable suspension formoterol compositions formulated at a concentration for direct administration to a subject in need thereof. As noted above, the Advisory Action acknowledges that the cited reference does not teach or suggest stable solution formoterol compositions formulated at this concentration. Thus, Applicant respectfully submits that the instant claims are not *prima facie* obvious over the teachings of Hochrainer *et al.*

Bartow *et al.* and the PDR do not cure the defects of Hochrainer *et al.*

Bartow *et al.* and the PDR entry for FLOVENT® do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. Neither Bartow *et al.* nor the PDR teach or suggest modification of the "active substance concentrate" or the "pharmaceutical preparation" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions of the instant claims. Bartow *et al.* and the PDR do not teach or suggest modifying the "active substance concentrate" or the "pharmaceutical preparation" of Hochrainer *et al.* such that the composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof, as required by the instant claims. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claims 1-64, 69-83, 87-89, 99-112 and 117-119 are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.

REJECTION OF CLAIM 93 UNDER 35 U.S.C. §103(a)

Claim 93 is rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.* (U.S. Patent No. 6,150,418) in view of Bartow *et al.* ((1998) *Drugs 55(2)*:303-322) and the Physician's Desk Reference (PDR) entry for fluticasone propionate, and further in view of the PDR entries of albuterol, accolate and Zyflo. Applicant respectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

The relevant law is discussed above.

Claim 93

Instant claim 93 is directed to the pharmaceutical composition of claim 1, as described above, further containing one or more of (a) to (j) as follows: (a) a ß2-adrenoreceptor agonist; (b) a dopamine (D2) receptor agonist; (c) an IL-5 inhibitor; (d) an antisense modulator of IL-5; (e) a tryptase inhibitor; (f) a tachykinin receptor antagonist; (g) milrinone or milrinone lactate; (h) a leukotriene receptor antagonist; (i) a 5-lypoxygenase inhibitor; or (j) an anti-IgE antibody.

Differences between the cited references and claim 93

Hochrainer *et al.*

The teachings of Hochrainer *et al.* are discussed in detail above. As noted above, the cited reference teaches stable formoterol aqueous suspension compositions that are not formulated at a concentration for direct administration to a subject in need thereof. Also, the Advisory Action admits that the instant claims, to the extent that they read on solution compositions, are patentable over the cited references. Therefore, Hochrainer *et al.* teaches away from instant claim 93 and instant claim 93 is not obvious over the teachings of Hochrainer *et al.*

Bartow *et al.* and the PDR do not cure the defects of Hochrainer *et al.*

Bartow *et al.*, the PDR entry for FLOVENT® and the PDR entries for albuterol, accolate and Zyflo do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized,

metered-dose aerosol units containing fluticasone propionate for oral inhalation. The PDR entries for albuterol, accolate and Zyflo teach that albuterol, accolate and Zyflo are all known to be effective in treating asthma.

Instant claim 93 is directed to a pharmaceutical composition of claim 1, further containing one or more of (a)-(j). Claim 1 recites that the pharmaceutical composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Neither Bartow et al. nor the PDR entries cited above teach or suggest modification of the "active substance concentrate" or the "pharmaceutical composition" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions of instant claim 93. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claim 93 is not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.

REJECTION OF CLAIMS 113-116, INSOFAR AS THEY READ ON IPRATROPIUM BROMIDE, UNDER 35 U.S.C. §103(a)

Claims 113-116, insofar as the read on ipratropium bromide, are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.*, Bartow *et al.* and the PDR, as above, and further in view of Hardman *et al.* (*Goodman Gilman's The Pharmacological Basis of Therapeutics*, 1996, page 665). Applicant respectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

The relevant law is discussed above.

Instant claims 113-116

Instant claim 113 is directed to the pharmaceutical composition of claim 1, as described above, further comprising an anticholinergic agent. Claims 114-116 are dependent on claim 113 and therefore incorporate all of the limitations of this claim.

Differences between the cited r f rences and the instant claims

Hochrainer *et al.*

The teachings of Hochrainer *et al.* are discussed in detail above. As noted above, the cited reference teaches stable formoterol aqueous suspension compositions that are not formulated at a concentration for direct administration to a subject in need thereof. Also, the Advisory Action admits that the instant claims, to the extent that they read on solution compositions, are patentable over the cited references. Therefore, instant claims 113-116 are not *prima facie* obvious over the teachings of Hochrainer *et al.*

Bartow *et al.*, the PDR and Hardman *et al.* do not cure the defects of Hochrainer *et al.*

Bartow *et al.*, the PDR entry for FLOVENT® and Hardman *et al.* do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. Hardman *et al.* teaches that ipratropium bromide is an anticholinergic agent useful in treating asthma.

Instant claims 113-115 (in so far as they read on ipratropium bromide) and 116 are directed to a pharmaceutical composition of claim 1, further containing an anticholinergic agent. Claim 1 recites that the pharmaceutical composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Neither Bartow *et al.*, the PDR nor Hardman *et al.* teach or suggest modification of the "active substance concentrate" or the "pharmaceutical preparation" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions of the instant claims. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claims 113-115 (in so far as they read on ipratropium bromide) and 116 are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.*, the PDR and Hardman *et al.*

REJECTION OF CLAIMS 113-116, INSOFAR AS THEY READ ON TIOTROPIUM BROMIDE, AND 120-121 UNDER 35 U.S.C. §103(a)

Claims 113-116, insofar as the read on tiotropium bromide, and 120-121 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.*, Bartow *et al.* and the PDR, as above, and further in view of Leckie *et al.* (*Novel Therapy of COPD*, abstract, January 2000). Applicant respectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

The relevant law is discussed above.

Instant claims 113-116 and 120-121

Instant claim 113 is directed to the pharmaceutical composition of claim 1, as described above, further comprising an anticholinergic agent. Claims 114-116, 120 and 121 are dependent on claim 113 and therefore incorporate all of the limitations of this claim.

Differences between the cited references and the instant claims

Hochrainer *et al.*

The teachings of Hochrainer *et al.* are discussed in detail above. As noted above, the cited reference teaches stable formoterol aqueous suspension compositions that are not formulated at a concentration for direct administration to a subject in need thereof. Also, the Advisory Action admits that the instant claims, to the extent that they read on solution compositions, are patentable over the cited references. Therefore, the instant claims 113-116 and 120-121 are not *prima facie* obvious over the teachings of Hochrainer *et al.*

Bartow *et al.*, the PDR and Leckie *et al.* do not cure the defects of Hochrainer *et al.*

Bartow *et al.*, the PDR entry for FLOVENT® and Leckie *et al.* do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. Leckie *et al.* teaches that tiotropium bromide is a known bronchiodilator employed in treating asthma.

Instant claims 113-115 (in so far as they read on tiotropium bromide) and 120-121 are directed to a pharmaceutical composition of claim 1, further containing an anticholinergic agent. Claim 1 recites that the pharmaceutical composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Neither Bartow *et al.*, the PDR or Leckie *et al.* teach or suggest modification of the "active substance concentrate" or the "pharmaceutical preparation" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions used in the instant claims. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claims 113-115 (in so far as they read on tiotropium bromide) and 120-121 are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.*, the PDR and Leckie *et al.*

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In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully Submitted,
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